Echocardiographic Findings and Follow-Up in Two HIV-Associated Pulmonary Arterial Hypertension Cases

Mircea Bajdechi[1]*, Adriana Gurghean[2], Georgiana-Elena Stoian[2], Dragos-Cosmin Zaharia[2], Tudor Constantinescu[2], Cristina-Elena Micu[1], Roxana Cernat[1], Irina Magdanela Dumitru[1] and Sorin Rugina[1]

[1]*Faculty of Medicine-"Ovidius" University of Constanta, Romania Spain*
[2]*Carol Davila" University of Medicine and Pharmacy of Bucharest, Romania*

Abstract

Pulmonary arterial hypertension associated with HIV infection is a separate entity. The prevalence is up to one thousand times higher than in general population. The mechanisms are multifactorial and incompletely elucidated. Echocardiography can suggest the diagnosis, but the gold standard method of diagnosing pulmonary arterial hypertension is right heart catheterization. We present clinical and paraclinical findings (NYHA, 6MWD, sPAP, RVGLS) and follow-up in two patients living with HIV, who are included in the Romanian National Program of Pulmonary Arterial Hypertension. In patients, the possible thromboembolism or left heart dysfunction were excluded. Each case has its own particularities, but both of them responded to treatment with sildenafil and improved clinical and paraclinical parameters. Mortality is high, usually due to right heart failure and pulmonary arterial hypertension is considered an independent predictor of death in HIV-infected patients. Co-management with both a Pulmonary Hypertension (PH) expert and a HIV expert is recommended.

Keywords: Pulmonary arterial hypertension • HIV • Cardiovascular • Echocardiography • Global longitudinal strain • Sildenafil

Abbreviations: HIV: Human Immunodeficiency Virus • NYHA: New York Heart Association • 6MWD: 6-Minute Walk Distance • sPAP: Systolic Pulmonary Arterial Pressure • RV GLS: Right Ventricle Global Longitudinal Strain

Introduction

Pulmonary Arterial Hypertension (PAH) associated with HIV infection is a separate entity and represents a special subgroup in the classification of pulmonary hypertension, developed by the European Society of Cardiology. Most of the studies reported a prevalence of 0.5%, confirmed by cardiac catheterization [1,2]. Echocardiographic studies showed higher PAH prevalence on these patients, between 6-14%, most of them being completely asymptomatic [3,4]. The occurrence of antiretroviral therapy did not change this prevalence.

The diagnosis should be suspected when signs and symptoms appear. Echocardiography can suggest the diagnostic and it is indicated in symptomatic patients or as a result of electrocardiographic abnormalities. The gold standard method of diagnosing pulmonary arterial hypertension is right heart catheterization. The treatment principles of HIV-associated pulmonary hypertension are similar to those of primary pulmonary hypertension, but there are some special considerations such as avoiding calcium channel blockers or avoiding co-administration of sildenafil with protease inhibitors [5].

PAH has a negative impact on the quality of life and it represents an independent mortality risk for these patients. Despite specific treatment, PAH was directly involved in 72% of deaths among the patients [6].

We present these two patients living with HIV, who are included in the Romanian National Program of Pulmonary Arterial Hypertension. For patients, the possible thromboembolism or left heart dysfunction were excluded. Each case has its own particularities, but both of them responded to treatment.

Case Report

Case I

A 31-year-old female from Bucharest, came to our cardiology department for evaluation. She was infected with HIV-1 by iatrogenic procedures and she is part of „The Romanian HIV cohort", which includes over 5000 patients that were infected during childhood between 1987-1989. In 2002 she was diagnosed with HIV infection and by then, the CD4 number was <200/μL. She refused specific therapy at that time. Since 2008, she has accepted the antiretroviral treatment and she has been treated with abacavir, lamivudine, lopinavir and ritonavir. Using this medication, the infection was controlled, with undetectable viremia and increasing CD4 cells number (Table 1).

In 2018 she was diagnosed with pulmonary arterial hypertension. At the diagnosis, she presented with shortness of breath, orthopnea associated with lower limb edema. The echocardiographic evaluation suggested high pulmonary arterial pressure and right cardiac catheterization confirmed pre-capillary pulmonary arterial hypertension. Since then, specific pulmonary arterial hypertension therapy with sildenafil combined with diuretic therapy including furosemide and spironolactone has been started. Also, the antiretroviral therapy has been changed and now she is on tenofovir, lamivudine and raltegravir and on this medication an improvement in clinical and paraclinical status was observed.

On this evaluation, the electrocardiogram showed sinus rhythm, 60 bpm, and right ventricular strain pattern. Echocardiography (Figure 1) revealed dilated right chambers, right ventricular dysfunction and high pulmonary arterial pressure with a normal left ventricle ejection fraction and normal mitral function.

Now she has an improved life quality, she is active at work and considers that she has a normal life.

Case II

A 46-year-old male from Bucharest came to our cardiology department for evaluation. In 2014, he was diagnosed with HIV-1 as a result of searching

Table 1. Infection controlled with undetectable viremia and increasing CD4 cells number.

Variables	2018	2019
HIV infection stage	**B3**	**B3**
CD4+ cells/μL	325	454
NYHA	IV	II
6MWD (meters/670)	-	400
Cardiac catheterization:		
• PAP(systolic/diastolic/mean) (mmHg)	81/31/54	
• RAP (mmHg)	10	
• PVR Wood units	16.33	
Echocardiografic findings:		
• sPAP (mmHg)	120	75
• TAPSE (mm)	10	15
• V GLS (-%)	-8	-14,4

NYHA: New York Heart Association; 6MWD: 6-min walk distance; NT pro-BNP: N-terminal prohormone of brain natriuretic peptide; sPAP: systolic pulmonary arterial pressure; RAP: right atrial pressure; PWP pulmonary artery wedge pressure; RV GLS: right ventricle global longitudinal strain.
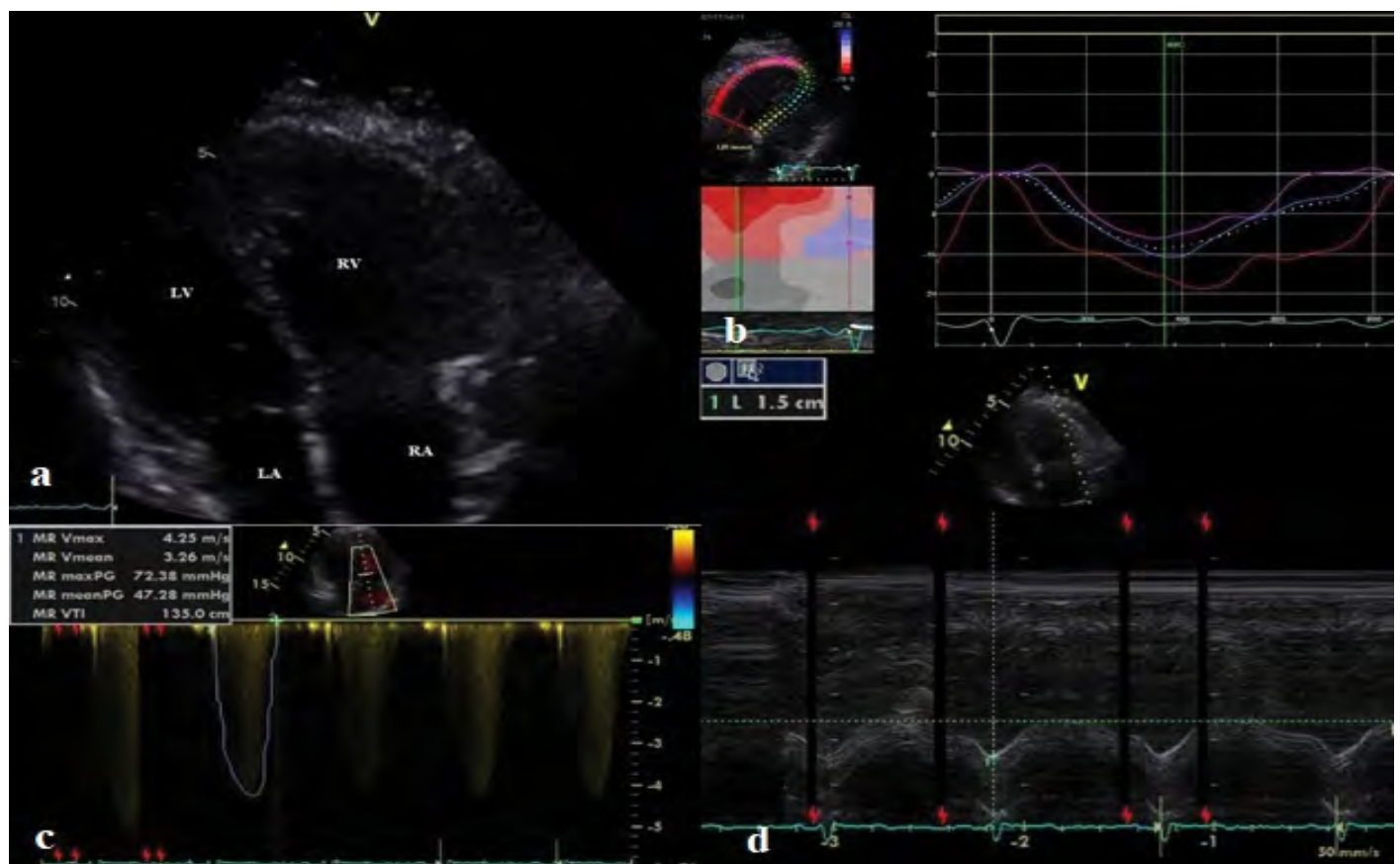

Figure 1. Transthoracic echocardiography: **a**-4 Chambers view: Dilated right chambers and right ventricle hypertrophy; **b**-Low right ventricle global longitudinal strain; **c**-High tricuspide valve gradient; **d**-Low tricuspid annular plane systolic excursion.

for the etiology of pulmonary arterial hypertension. He acquired the infection by sexual contact. At pulmonary arterial hypertension diagnosis time, his symptoms were fatigue and dyspnea at medium effort. The echocardiography revealed high pulmonary arterial pressure. Right cardiac catheterization confirmed pre-capillary pulmonary arterial hypertension. Since then, specific PAH therapy with sildenafil combined with diuretic therapy including furosemide and spironolactone and antiretrovirals like lamivudine, zidovudine and raltegravir has been started. The patient has intermittent adherence on antiretroviral therapy and discontinued the treatment for several months between 2016 and 2017.

Echocardiography (Figure 2) showed dilated right chambers, right ventricular dysfunction and pulmonary hypertension with a normal left ventricle function and normal mitral function.

Therapeutic compliance in the last three years has improved the clinical and paraclinical status, without requiring hospitalization (Table 2).

Discussion

These two patients are included in the Romanian National Program of Pulmonary Arterial Hypertension. In both patient, the possible thromboembolism or left heart dysfunction were excluded. Each case has its own particularities, but both of them responded to treatment. Although, the occurrence of antiretroviral therapy has not changed the prevalence of PAH in persons living with HIV, it appears that interruption of antiretroviral therapy in patients who have already developed the disease may exacerbate the symptoms.

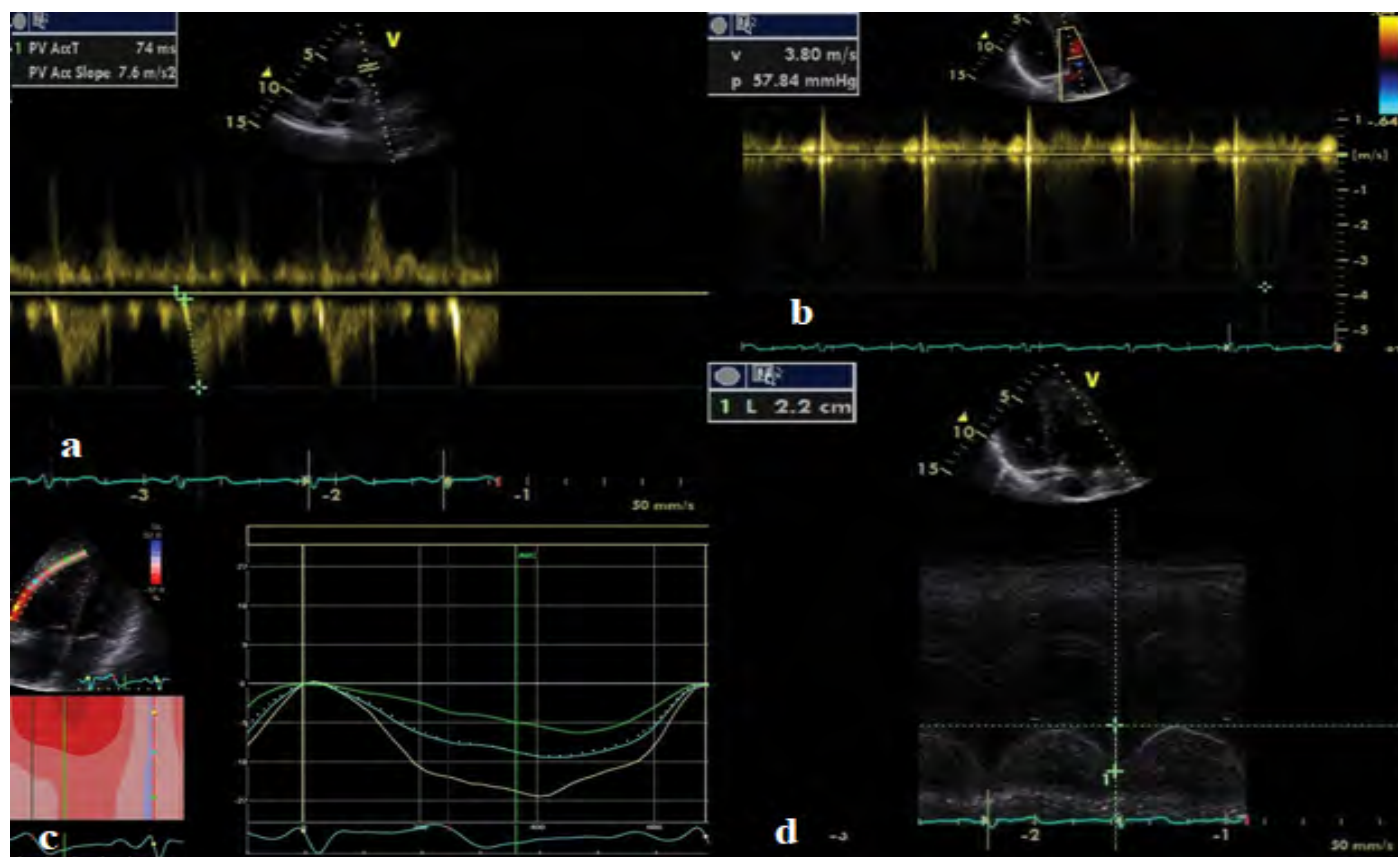Pulmonary arterial hypertension has multiple and incompletely elucidated

Figure 2. Transthoracic echocardiography **a**-Low pulmonary acceleration time; **b**-High tricuspide valve gradient; **c**-Low right ventricle global longitudinal strain; **d**-Normal tricuspid annular plane systolic excursion.

Table 2. Therapeutic compliance in the last three years has improved the clinical and paraclinical status, without requiring hospitalization.

Variables	2014	2015	2016	2017	2020
HIV infection stage	B2	B2	B2	B2	B2
CD4+ cells/uL		355			580
NYHA	III	II	I-II	II	I
6MWD (meters/650)	565	621	650	550	650
Cardiac catheterization:					
• PAP (systolic/diastolic/mean) (mmHg)	97/30/59				
• RAP (mmHg)	9				
• PWP (mmHg)	9				
Echocardiografic findings:					
• sPAP (mmHg)	77	63	49	105	70
• TAPSE (mm)	14	25	25	20	22
• PVAT (msec)	80			72	74
• RV GLS (-%)					-17

NYHA: New York Heart Association; 6MWD: 6-Min Walk Distance; NT pro-BNP: N-Terminal Prohormone of brain Natriuretic Peptide; sPAP: Systolic Pulmonary Arterial Pressure; RAP: Right Atrial Pressure; PWP Pulmonary Artery Wedge Pressure; RV GLS: Right Ventricle Global Longitudinal Strain.

mechanisms, but inflammation plays the central role. One particular element is that dendritic cells from the pulmonary artery maintain on their surface the virus, releasing cytokines (IL-1 beta, IL-6, TNF alpha, platelet growth factor) leading to local tissue injury. Systemic cytokine release has procoagulant effect, increases the expression of endothelial adhesion molecules and accumulation of inflammatory cells in the pulmonary artery. For sure, not only the release of cytokines is responsible for the development of PH in these patients, because their values are high in most of them and only a small part develop PH. Recent studies showed that even in the absence of pulmonary arterial hypertension, a degree of remodelling of the right heart has been described in a proportion of HIV-infected patients [7].

The prevalence of Pulmonary Arterial Hypertension (PAH) in HIV-infected patients is up to one thousand times higher than in general population.

Predictive factors for the development of pulmonary hypertension are feminine gender, hepatitis C infection, cocaine use and HIV viral load [8]. Among the users of intravenous drugs, the prevalence of pulmonary hypertension can reach 59% [6].

Despite the high prevalence of pulmonary hypertension in these patients compared to the general population, the guideline does not recommend echocardiographic screening in these patients (IIIC). Cardiac ultrasonography should be performed as a result of electrocardiographic changes or in symptomatic patients. However, the recommendations of the Sixth World Symposium on Pulmonary Hypertension propose echocardiographic evaluation in symptomatic patients or who have several risk factors (female sex, HCV infection, Nef or Tat mutations, Afro-americans). Paraclinical changes of right overload may appear early, so evaluation of these patients by new paraclinical techniques (speckle tracking) should be done [9].

The treatment principles of HIV-associated pulmonary hypertension are similar to those of primary pulmonary hypertension, but there are some special considerations such as avoiding calcium channel blockers [5].

The patients with WHO functional class I do not require specific PH treatment and they should be monitored every three to six months. WHO functional class II-IV should be referred to a specialized PAH center. In these two cases, sildenafil improves clinical and paraclinical parameters. Sildenafil should be avoided in those receiving a pharmacologic boosting agent such as ritonavir or cobicistat and it can significantly decreases protease inhibitor levels [10]. In the literature, other phosphodiesterase inhibitors (tadalafil or vardenafil) have not been adequately studied in these patients.

Conclusion

Pulmonary Arterial Hypertension (PAH) associated with HIV infection is a separate entity. The mechanisms are multifactorial and incompletely elucidated. The prevalence is up to one thousand times higher than in general population. Sildenafil is the treatment of choice, but interaction with certain antiretroviral drugs should be considered. Mortality is high, usually due to right heart failure and PAH is considered an independent predictor of death in HIV-infected patients.

Conflict of Interests

The authors declare no conflict of interest.

References

1. Barbaro, Giuseppe and Erika Ferrari Rafael da Silva. "Cardiovascular complications in the acquired immunodeficiency syndrome." *Rev Assoc Med Bras* 55 (2009): 621-630.

2. Sitbon, Olivier, Caroline Lascoux-Combe, Jean-François Delfraissy, Patrick Yeni and Francois Raffi, et al. "Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era." *Am J Respir Crit Care Med* 177 (2008): 108-113.

3. L'Huillier, Arnaud Gregoire, Klara Maria Posfay-Barbe, Hiba Pictet and Maurice Beghetti. "Pulmonary arterial hypertension among HIV-infected children: results of a national survey and review of the literature." *Front Pediatr* 3 (2015): 25.

4. Schwarze Zander, Stefan Pabst, Christoph Hammerstingl and James Ohlig, et al. "Pulmonary hypertension in HIV infection: a prospective echocardiographic study." *HIV Med* 16 (2015): 578-582.

5. Montani, David, Laurent Savale, Delphine Natali and Xavier Jais, et al. "Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension." *Eur Heart J* 31 (2010): 1898-1907.

6. Nunes, Hilario, Marc Humbert, Olivier Sitbon and Jane Morse, et al. "Prognostic factors for survival in human immunodeficiency virus–associated pulmonary arterial hypertension." *Am J Respir Crit Care Med* 167 (2003): 1433-1439.

7. Güvenç, Rengin Çetin, Nurgül Ceran, Tolga Sinan Güvenç and Hacer Ceren Tokgoz, et al. "Right Ventricular Hypertrophy and Dilation in Patients With Human Immunodeficiency Virus in the Absence of Clinical or Echocardiographic Pulmonary Hypertension." *J Card Fail* 24 (2018): 583-593.

8. Quezada, Maribel, Luz Martin-Carbonero, Vicente Soriano and Eugenia Vispo, et al. "Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up." *AIDS* 26 (2012): 1387-1392.

9. Simonneau, Gerald, David Montani, David Celermajer and Christopher Denton, et al. "Haemodynamic definitions and updated clinical classification of pulmonary hypertension." *Eur Respir J* 53 (2019).

10. Pergola, Valeria, Cesare Caruso, Roberto Gnarini and Serafino Fazio, et al. "Efficacy of sildenafil in HIV-related pulmonary arterial hypertension." *J Cardiovasc Med* 16 (2015): S136-S137.